REMARKS

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and the following remarks.

It is acknowledged that the foregoing amendments are submitted after final rejection. However, because the amendments do not introduce new matter or raise new issues, and because the amendments either place the application in condition for allowance or at least in better condition for appeal, entry thereof by the Examiner is respectfully requested.

I. Status of the Claims

Claims 1-23, 25 and 29 were pending in the application, with claims 1 and 23 being the independent claims. Claim 1 is amended and claim 30 is newly added. Thus, upon entry of this paper, claims 1-23, 25 and 29-30 are currently pending and under active consideration.

Support for the term "wherein the proportion of the label-isotope of at least 50 metabolites of the biological sample is increased to at least 80% of the total of all isotopes of the element" can be found throughout the specification. Specifically, support can be found on page 9, lines 21 to 26 and page 10 lines 25 to 29 of the specification.

II. The Rejections Under 35 U.S.C. § 103(a)

The Office Action, at pages 2-5, rejects claims 1, 5-13, 15 and 20-22 under 35 U.S.C. § 103(a) as allegedly being obvious over US Patent Application Publication No. 2003/0180710 A1 to Lee *et al.* ("Lee"). Applicants respectfully traverse this ground of rejection.

A. Current Obviousness Standard

The Supreme Court recently reaffirmed the Graham factors for determining obviousness in *KSR Int'l Co. v. Teleflex Inc.* (550 U.S. 398 (2007)). The Graham factors, as outlined by the Supreme Court in *Graham et al. v. John Deere Co. of Kansas City et al.*, 383 U.S. 1 (1966), are: 1) determining the scope and contents of the prior art; 2) ascertaining the differences between the claimed invention and the prior art; 3) resolving the level of ordinary skill in the pertinent art; and 4) evaluating evidence of secondary consideration. The

Supreme Court recognized that a showing of "teaching, suggestion, or motivation" to combine the prior art to meet the claimed subject matter could provide a helpful insight in determining whether the claimed subject matter is obvious under 35 U.S.C. § 103(a), and held that the proper inquiry for determining obviousness is whether the improvement is more than the predictable use of prior art elements according to their established functions. The Court noted that it is "important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the [prior art] elements" in the manner claimed, and specifically stated:

> Often, it will be necessary . . . to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was ***an apparent reason to combine the known elements in the fashion claimed*** by the patent at issue. To facilitate review, this analysis should be made explicit.

KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 418 (2007) (emphasis added). As discussed below, the cited art cannot render the claimed invention obvious.

B. Isotope of Carbon

As an initial matter, the Office states that claim 1 requires that cells take up a labeled compound such that its metabolites are saturated with the isotope of the compound. Additionally, the Office states that "Since ^{12}C is an isotope of carbon, the claim as written may require revision to clarify applicant's intent."

Applicants define the term "isotopic labeling" on page 9 line 21 to page 10 line 6. Specifically, applicants define "isotopic labeling" to "be understood to refer to compounds that are labeled with an isotope that is not the main isotope of the element of said isotope." (See specification page 9 lines 21-22). Thus, the "isotopically labeled metabolizable compound" would not include ^{12}C, even though ^{12}C is an isotope of carbon, because ^{12}C is the main isotope of the element.

C. The Rejection over Lee

1. The Cited Prior Art Fails to Teach or Suggest Each and Every Element of the Claimed Invention

Lee discloses metabolic flux studies. These studies are fundamentally different from the claimed invention. Specifically, flux studies require 1) partial labeling of the metabolites, and 2) monitoring the kinetics of stable isotope enrichement through analysis of mass isotopomer distributions. Thus, these metabolic flux studies act in a similar fashion to a pulse chase type experiment.

In contrast to flux studies, the claimed invention requires: 1) saturation labeling of the metabolites and 2) comparison of the labeled metabolites to a second biological sample. Therefore, the claimed invention does not reveal kinetic properties. To the contrary, the idea of the present invention is to achieve an as complete as possible labeling in order to achieve an as complete as possible set of labeled metabolites that can be compared with metabolites of a second biological sample. Specifically, "substantially **all of the metabolites** to be analyzed contain the isotope label." (Specification, page 10 second paragraph)(emphasis added) Thus, full labeling of the metabolites represents an endpoint, and does not represent a starting point.

In an effort to advance prosecution of this application and without acquiescing to the propriety of this rejection, Applicants have amended the claims to include description that "at least 50 metabolites of the biological sample is increased to at least 80% of the total of all isotopes of the element." As such, Applicants believe that the claims now specifically capture the differences between conventional flux studies and the claimed invention.

2. Combination of the Claimed Elements Would Render Lee Inoperable

The Office Action, at page 3, contends "Lee teaches methods of studying metabolism and that precursors may be partially or uniformly labeled. Precursors are metabolized, whether they are partially or uniformly labeled, and metabolites can be detected and

quantified in an analysis of isotopomers, which is also taught by Lee." (Office Action, page 3).

The Examiner is reminded that "[i]f proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. *In re Gordon*, 733 F.2d 900, 211 USPQ 1125 (Fed. Cir. 1984)." MPEP 2143.01 Section V.

In an effort to advance prosecution of this application and without acquiescing to the propriety of this rejection, Applicants have amended the claims to bring out the distinction between conventional flux techniques and the claimed invention. Specifically, it would not be possible to detect influences of drugs or substances on the metabolism as intended by the method of Lee if Lee employed the strategy of the amended claimed invention. Lee states that "[t]he label system of the invention can clearly differentiate and characterize these pathways and their responses to drug treatments in a specific and effective manner in a simple series of labeling and drug treatment studies." (Lee paragraph [0035]) Additionally, Lee states "[t]he invention makes it possible to track enzymatic modification of the precisely labeled precursor molecule as it makes specific arrangements in the positions and amounts of the stable isotope incorporated into subsequent bio-molecules throughout the metabolome." (Lee paragraph [0037])

If Lee were to use a completely saturated metabolite where in at least 50 metabolites of the biological sample is increased to at least 80% of the total of all isotopes of the element, Lee would not be able to determine the specific arrangements in the positions and the amounts of the stable isotope incorporated into subsequent bio-molecules. Furthermore, if a substantial number of all the metabolites were labeled, Lee would have nothing to read out. Lee is based on a flux study which first labels the metabolite and then chases with unlabeled metabolite, then follows the label to downstream metabolites. In contrast, the claimed invention saturates the metabolite and then compares this to an unlabeled sample. As such, Lee's invention would be rendered inoperable if modified to conform with the amended claimed invention.

Thus, at least for the reasons stated above, the rejection is improper. Reconsideration and withdrawal of this ground of rejection are therefore respectfully requested.

D. The Rejection over Lee in view of Abramson

The Office Action, at pages 5-6, rejects claims 2-4 under 35 U.S.C. § 103(a) as allegedly being obvious over US Patent Application Publication No. 2003/0180710 A1 to Lee *et al.* ("Lee") in view of US Patent Application Publication No. 2003/0077572 A1 to Abramson *et al.* ("Abramson"). Applicants respectfully traverse this ground of rejection.

Abramson does not remedy the deficiencies of Lee described above. In fact, Abramson discloses differential labeling of two cell populations, each labeled to a different extent. Thus, Abramson fails to teach or suggest saturated labeling.

Accordingly, the rejection is improper. Reconsideration and withdrawal of this ground of rejection are therefore respectfully requested.

E. The Rejection Over Lee in view of Kasper

The Office Action, at pages 6-7, rejects claim 14 under 35 U.S.C. § 103(a) as allegedly being obvious over US Patent Application Publication No. 2003/0180710 A1 to Lee *et al.* ("Lee") in view of US Patent Application Publication No. 2005/0112706 A1 to Kasper. Applicants respectfully traverse this ground of rejection.

Kasper discloses methods for determining androgen responsiveness in a sample using bioassays. Kasper fails to teach or suggest cell labeling, let alone saturated labeling. Thus, Kasper fails to remedy the deficiencies of Lee.

Accordingly, the rejection is improper and should be withdrawn.

F. The Rejection Over Lee in view of Birkemeyer

The Office Action, at pages 7-8, rejects claims 16-17 under 35 U.S.C. § 103(a) as allegedly being obvious over US Patent Application Publication No. 2003/0180710 A1 to Lee

et al. ("Lee") in view of Birkemeyer *et al.* 2003 J. Chromatography A 993: 89 ("Birkemeyer"). Applicants respectfully traverse this ground of rejection.

Birkemeyer discloses gas chromatography analysis of phytohormones. The reference fails to teach or suggest isotope labeling, let alone saturated labeling, and thus fails to remedy the deficiencies of Lee described above.

Thus, the rejection is improper. Reconsideration and withdrawal of this ground of rejection are therefore respectfully requested.

G. The Rejection Over Lee in view of Hellerstein-APEM

The Office Action, at pages 8-9, rejects claims 18-19 under 35 U.S.C. § 103(a) as allegedly being obvious over US Patent Application Publication No. 2003/0180710 A1 to Lee *et al.* ("Lee") in view of MK Hellerstein and RA Neese 1999 *American J. Physiol. Endocr. Metab. 276*: 1146- 1170 ("Hellerstein-APEM"). Applicants respectfully traverse this ground of rejection.

Hellerstein-APEM fails to remedy the deficiencies of Lee described above, as the reference provides a review of mass isotopomer distribution. Accordingly, the rejection is improper and should be withdrawn.

H. The Rejection Over Lee in view of Hellerstein

The Office Action, at page 9, rejects claim 25 under 35 U.S.C. § 103(a) as allegedly being obvious over US Patent Application Publication No. 2003/0180710 A1 to Lee *et al.* ("Lee") in view of US Patent Application Publication No. 2004/00811994 A1 to Hellerstein ("Hellerstein"). Applicants respectfully traverse this ground of rejection.

Hellerstein discloses biochemical methods for assessing metabolic fitness. The reference fails to teach or suggest cell labeling, and thus fails to remedy the deficiencies of Lee described above. Accordingly, the rejection is improper and should be withdrawn.

I. The Rejection Over Lee in view of Evans

The Office Action, at pages 9-10, rejects claim 23 under 35 U.S.C. § 103(a) as allegedly being obvious over US Patent Application Publication No. 2003/0180710 A1 to Lee *et al.* ("Lee") in view of US Patent No. 5,532,206 to Evans *et al.* ("Evans"). Applicants respectfully traverse this ground of rejection.

Evans does not remedy the deficiencies of Lee described above as the patent discloses application of C-16,17- dihydro gibberellin to plants.

Accordingly, the rejection is improper and should be withdrawn.

J. The Rejection Over Lee in view of Evans and Further in view of Hellerstein

The Office Action, at page 10, rejects claim 29 under 35 U.S.C. § 103(a) as allegedly being obvious over US Patent Application Publication No. 2003/0180710 A1 to Lee *et al.* ("Lee") in view of US Patent No. 5,532,206 to Evans *et al.* ("Evans") and further in view of US Patent Application Publication No. 2004/00811994 A1 to Hellerstein ("Hellerstein"). Applicants respectfully traverse this ground of rejection.

As discussed above, none of the cited references teaches or suggest the claimed invention. Thus, the rejection is improper.

Reconsideration and withdrawal of this ground of rejection are therefore respectfully requested.

CONCLUSION

All of the stated grounds of objection and rejection have been properly traversed or rendered moot. Thus, the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing or a credit card payment form being unsigned, providing incorrect information resulting in a rejected credit card transaction, or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, applicants hereby petition for such extension under 37 C.F.R. § 1.136 and authorize payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

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By _____

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